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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,292	12/01/2003	Juan Armendariz Borunda	061537-0036US	4513

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/724,292	ARMENDARIZ BORUNDA ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,24,28-30 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24,28-30 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 4-28-08 has been entered. Claims 22 and 24 have been amended. Claims 25-27 have been canceled. Claims 22, 24, 28-30 and 32-34 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 22, 24, 28-30 and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendment filed 4-28-08 necessitates this new ground of rejection.

The phrase "wherein the composition is suitable for intravenous administration" in newly amended claim 22 is vague and renders the claim indefinite. It is unclear what kind of composition is "the composition suitable for intravenous administration". The specification fails to define such composition. Claims 24, 28-30 and 32-34 depend from claim 22 but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' amendment filed 4-28-08 necessitates this new ground of rejection.

The phrase "wherein the composition is suitable for intravenous administration" in newly amended claim 22 is considered new matter. Applicants fail to point out where the support is in the specification for the phrase "wherein the composition is suitable for intravenous administration". The specification fails to provide sufficient support for the phrase set forth above. Thus, the phrase "wherein the composition is suitable for intravenous administration" is considered new matter.

5. Claims 22, 24, 28-30 and 32-34 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing fibrosis in hepatic cirrhosis by injecting via iliac vein a replication defective adenovirus vector AdMMP-8 expressing human MMP-8 protein under the control of CMV promoter as disclosed in the cited references Siller-Lopez et al., 2004 (Gastroenterology, Vol. 126, p. 1122-1133) and Garcia-Banuelos et al., 2002 (Gene Therapy, Vol. 9, p. 127-134) (amendment filed on 10-31-07), does not reasonably provide enablement for a pharmaceutical composition comprising recombinant adenovirus expressing the proteins as recited in the claims under the control of various promoters, and a method for treating various fibrotic disorders by using said pharmaceutical composition via various administration routes or administration to various organs. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reason set forth in the preceding Official action mailed 1-28-08. Applicant's arguments filed 4-28-08 have been fully considered but they are not persuasive.

Applicants argue that metalloproteases degrade collagen with each metalloprotease capable of degrading multiple types of collagen, and the truncated receptor for TGF-beta type II is useful to re-establish normal liver function. The specification illustrates the success of the claimed invention in increasing the presence of expressed protein in a fibrotic liver through a recombinant adenovirus. Genes other than MMP-8 are not unpredictable in their effect and will not create undue experimentation (amendment, p. 5-6). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-28-08. The specification fails to disclose how the truncated receptor for TGF-beta II is useful to re-establish normal liver function and how that is correlated to treating hepatic fibrosis. Different therapeutic proteins have different amino acid sequences and their biological functions would differ. MMP-1, 2, 8, 9, 13 and truncated receptor of TGF-beta type II are different proteins and having diverse biological functions. Even MMP-8 proteins derived from different organisms could have different biological functions. The specification fails to provide adequate guidance and evidence for whether the claimed therapeutic protein or combination of therapeutic proteins would be able to treat hepatic fibrotic diseases or disorders via intravenous administration in vivo. It was known in the art that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine

experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention and even same short stretch of amino acid sequence can show diverse biological functions while surrounded by different background amino acid sequences. There is no evidence of record that the claimed adenoviral vector expressing the recited therapeutic protein or combination of therapeutic proteins would be able to provide therapeutic effect in vivo so as to treat hepatic fibrotic diseases or disorders. Therefore, one skilled in the art at the time of the invention would not know how to use the claimed pharmaceutical composition comprising adenoviral vector to treat hepatic fibrotic diseases or disorders via intravenous administration in vivo and require undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 22 and 28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Fernandez et al., 1998 (Surgery, Vol. 124, p. 129-136) in view of Hasty et al., 1990 (The Journal of Biological Chemistry, Vol. 265, No. 20, pp. 11421-11424) and is repeated for the reason set forth in the preceding Official action mailed 1-28-08. Applicant's arguments filed 4-28-08 have been fully considered but they are not persuasive.

Applicants argue that Fernandez and Hasty fail to disclose or suggest a composition for intravenous administration to treat liver fibrosis and both are silent about the unitary doses of viral particles or recombinant adenoviral vectors for intravenous administration. Both reference fail to disclose or suggest serotype Ad5 with deletion at E1 and inserted with a DNA sequence regulated by a ubiquitous promoter, a tissue-specific promoter or a combination thereof (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-28-08. It is noted that claims 22 and 28 are product claims drawn to a composition comprising a unitary dose of viral particles of recombinant adenoviral vectors. Fernandez teaches preparation of a recombinant adenovirus vector AdMMP-3 expressing MMP-3 protein under the control of CMV promoter, which is a ubiquitous promoter. The dose of $1x10^9$ pfu as taught by Fernandez is in the range of $1x10^7$ pfu to $1x10^{14}$ pfu. The buffer solution containing the adenovirus vector is considered a pharmaceutically acceptable carrier. Hasty teaches the cDNA sequence encoding the human neutrophil collagenase, i.e. MMP-8. Fernandez and Hasty teach the claimed composition comprising the recombinant adenoviral vector. Whether the claimed composition is used for intravenous administration to treat liver fibrosis is

irrelevant to the claimed composition. Further, serotype Ad5 and deletion of E1 region to produce replication-deficient adenoviral vector were well known in the art and are obvious to one of ordinary skill in the art at the time of the invention. Thus, the claims remain rejected under 35 U.S.C. 103(a).

9. Claims 22 and 33 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al., 1996 (Matrix Biology, Vol. 15, pp. 383-395) and is repeated for the reason set forth in the preceding Official action mailed 1-28-08. Applicant's arguments filed 4-28-08 have been fully considered but they are not persuasive.

Applicants argue that Baker does not disclose or suggest administering a composition intravenously for recombinant expression in the liver and an effective dose for the intravenous administration (amendment, p. 8-9). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-28-08. It is noted that claims 22 and 33 are product claims drawn to a composition comprising a unitary dose of viral particles of recombinant adenoviral vectors. Baker teaches preparation of an adenoviral vector containing the gene sequence of MMP-9 under the control of CMV promoter, which is a ubiquitous promoter, and determining effective dose is routine optimization of a result-effective variable and is obvious to one of ordinary skill. Baker teaches the claimed composition comprising the recombinant adenoviral vector. Whether the claimed composition is used for intravenous administration to treat liver fibrosis is irrelevant to the claimed composition. Thus, the claims remain rejected under 35 U.S.C. 103(a).

Conclusion

No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.
/Shin-Lin Chen/

Primary Examiner, Art Unit 1632